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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,945	02/16/2005	Farhad Parhami	58086-241892	3129

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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
12/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,945	PARHAMI, FARHAD	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 15-41* is/are pending in the application.

4a) Of the above claim(s) *4,5,9,10,18,22 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-8, 11-17, 19-21, 23-26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09-24-2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09-23-2009 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-12 and 15-41 are pending. Claims 1-5, 7-10, 12, 16-18, 20-23, 25-28, 30, 31, 33,34, and 41 have been amended by Applicants' amendment filed on 09-23-2009. Claims 4, 5, 9, 10, 18, 22 and 27 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, and claims 29-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The examiner acknowledges receiving the Declaration under 37 C.F.R. § 1.132 signed by Dr. Farhad Parhami ("the Parhami Declaration" therefrom).

Therefore, claims 1-3, 6-8, 11-17, 19-21, 23-26 and 28 are currently under examination to which the following grounds of rejection are applicable.

Response to arguments

Rejections maintained in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 103(a)

Claims 1-3, 6-8, 11-17, 19-21, 23-26 and 28 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Paralkar et al., US Publication no. 20040176423 (Date of Publication September 9, 2004), in view of Parish et al., (1995, Lipids, pp. 247-251) and further in view of Wang et al. (Clinical Orthopaedics and Related Research, 2000, 370: 295-310).

Paralkar et al. teaches *in vitro* and *in vivo* methods for enhancing bone formation in mammals, including humans, comprising administration of compositions comprising 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors such as statins and prostaglandin agonists (p. 1, paragraph [0010]). Indeed, Paralkar et al. exemplifies enhanced expression of mRNA for bone morphogenic protein-2 (BMP-2) (e.g., BMP2 expression induces osteoblast differentiation) in cultured murine 2T3 cells or human MG-63 bone cells (i.e., osteo-progenitor human osteoblast) exposed to statins statins (p.3, paragraphs [0051] [0053]). Cell culture of progenitor osteoblastic cells with statin stimulates bone formation *in vitro* and enhances osteoblast cell numbers at all stages of differentiation (p. 1, paragraph [0011]; p.3 paragraph [0051]). Paralkar et al. discloses that compounds which inhibit the enzyme HMG-CoA reductase include the compounds known as statins including mevastatin, lovastatin, pravastatin, velostatin, simvastatin, fluvastatin, cerivastatin and mevastatin, dalvastatin and fluindostatin and atorvastatin (page 3, paragraph [0041]).Paralkar et al. also teaches methods of stimulating mammalian cells to express biological differentiation markers (p.3, paragraph [0053]). **(Current claim 6, in part)**. Paralkar et al. teaches treatment with a combination of active ingredients including prostaglandins, estrogen receptor modulators and peptide hormones for inhibition of bone resorption which may be administered separately (page 1,

paragraph[0018]); page 6,paragraph [0088]). Paralkar et al. describes effective therapeutic does of statins that are titrate to achieve bone mass augmentation)(p. 5,paragraphs [0077]-[0078]). Furthermore, Paralkar et al. discloses that bisphosphonates are anti-resorptive agents used to combat osteoporosis and contemplates their administration with a HMG-CoA reductase inhibitor as a therapy for bone conditions (p. 1, paragraphs [0007] and [0018]) (**Current claims 23 and 28**).

Paralkar et al. does not specifically teach osteblastic differentiation with one oxysterol.

However, at the time the invention was made, Parish et al., discloses that side-chain oxysterols are known to be potent inhibitors of HMG-CoA reductase, including sterols (e.g., derivatives of cholesterol) having hydroxyl functions in the side chain specifically side-chain hydroxylation at 20 α- and 22R-positions (All document, particularly Abstract, p. 248, col. 2; p. 250, col. 1, paragraph 2) . (**Current claims 2, 7, 15, 16, 19, 20, 24 and 25**). In addition, Paralkar et al., discloses at page 250, Tables 1-3, the relative potency of a wide number of oxysterols that inhibit HMG-CoA reductase, which exhibit synergism in the reduction of the levels of HMG-CoA reductase activity (p. 250, col. 2, paragraph 2) (Current claims **3, 8, 17, 21 and 26**).

The combined references fail to teach mammalian mesenchymal stem cells.

However, at the time the invention was made, Wang et al. teaches that treatment with statins (e.g., lovastatin) inhibits adipocyte differentiation and induces osteoblastic differentiation of mouse MSCs (e.g., pluripotent mesenchymal cells, D1) as indicated by markers such as alkaline phosphatase activity, osteocalcin mRNA and cAMP production

(**claims 11 and 12**) (Abstract, p. 297, col. 1 last paragraph; col. 2, paragraph 1; p. 299, col. 1; p. 300, col. 1; p. 307, col. 2, paragraph 1).

Therefore, in view of the benefits of enhancing bone formation in mammalian cells by using inhibitors of HMG-CoA reductase such as statins, it would have been *prima facie* obvious for one of ordinary skill in the art, on teachings provided by the combined cited references, to modify the composition of Paralkar et al. to replace statins with derivatives of cholesterol with side-chain hydroxylation at 20 α- and 22R-positions, particularly because Parish et al., discloses that it is well known in the art that oxysterols repress HMG-CoA reductase activity. The substitution of statins in the method of Paralkar et al., by side-chain oxysterols hydroxylated at 20 α- and 22R-positions would achieve the predictable results of inducing osteoblastic differentiation as both compounds repress the same HMG-CoA reductase and thus reduced sterol biosynthesis. Likewise, it would have been *prima facie* obvious for one of ordinary skill in the art, in an attempt to optimize reduced levels of HMG-CoA reductase activity, to combine any of the disclosed side-chain oxysterols inhibiting HMG-CoA reductase activity as Parish et al., teaches their synergism reducing this enzyme activity. Moreover, it would have been *prima facie* obvious as a matter of design of choice, to use MSC which are pluripotent cell lines from bone marrow stroma to achieve the predictable result of inducing osteoblasts differentiation and inhibiting adipocyte differentiation, particularly because Wang et al. successfully demonstrates decreased lipid accumulation while maintaining a osteoblastic phenotype in MSCs after treatment with statins and steroids. One of ordinary skill in the art would have had a reasonable expectation of success in generating a method to induce osteblastic differentiation of MSC by treating said cells with at least one oxysterol as

evidenced by the production of said method in the instant specification by following the combined teachings of Paralkar, Parish and Wang.

Response to Applicants' arguments as they apply to rejection of 1-3, 6-8, 11-17, 19-21, 23-26 and 28 under 35 U.S.C. 103(a)

At pages10-12 of the remarks filed on 09-23-2009 insofar as the disclosure of Paralkar, Applicants essentially argue that: 1) the fact that certain statins, which are HMG-CoA reductase inhibitors, induce osteoblastic differentiation of osteo-progenitor human osteoblast MG-63 bone cells, does not suggest that oxysterols can enhance osteoblastic differentiation, 2) there is a logical disconnect to the allegation that oxysterols could be substituted for statins because Paralkar did not demonstrate a causal relationship between the ability of statins to inhibit HMG-CoA reductase and their allege ability to induce osteoblastic differentiation, 3) it would have been unpredictable at the time of filing whether two different inhibitors of HMG-CoA reductase would have the same effect, e.g., osteoblastic differentiation, 4) post filing art by Parhami et al (Nov 2002, J. *Bone and Miner Res* pp. 1997-2003) teaches that mevastatin which is a HMG-CoA reductase inhibitor, disclosed by Paralkar, and should be expected to induce osteoblastic differentiation of mammalian mesenchymal stem cells (MSCs), does not significantly suppress the expression of and activity of ALP, a key enzyme involved in differentiation and mineralization of osteoblastic cells, and 5) the inventors point out in the Parhami Declaration that the osteogenic effect of the stains discussed by Paralkar is a result of BMP-2 expression whereas the osteogenic effect of oxysterols is not a result of BMP-2 expression but rather mediated by aspects of the hedgehog signaling pathway. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). None of the references has to teach each and every claim limitation. If they did, this would have been anticipation and not an obviousness-type rejection.

Regarding 2), 3) and 4), the fact that the disclosure of Parhami et al., (2002) teaches two inhibitors of HMG-CoA reductase, i.e., mevastatin and mevinolin, that suppress expression and activity of ALP, a key enzyme involved in differentiation and mineralization of osteoblastic cells (Parhami, page 1999, Fig. 1), and the fact that mevastatin is one of the statins recited by Paralkar are not disputed. However, mevastatin and not metavastin, as stated by Applicants, is one of the many statins recited by Paralkar. The fact that mevastatin does not promote osteoblastic differentiation does not preclude the skilled artisan from having a reasonable expectation of successfully making and using the claimed invention using the genus of statins including simvastatin, pravastatin, cerivastatin, velostatin, fluvastatin, lovastatin, dalvastatin, fluindostatin, atorvastatin, and atorvastatin calcium from being without undue experimentation. Indeed, he art as a whole at the time the invention was made teaches statins as inducers of osteoblastic differentiation. For example, Mundy, et al., (1999, Science, pp. 1946 – 1949) teaches that statins, in particularly lovastatin, simvastatin, mevastatin, and fluvastatin are considered especially useful in that they not only increase the formation of new bone, but also enhance the accumulation of mature osteoblasts, the cells involved in new bone growth. Note that Paralkar lists lovastatin simvastatin, mevastatin and fluvastatin.

Likewise, Garrett et al., summarizes the role of statins at the time the invention was made, enhancing bone formation (Garrett et al., Feb. 2002, *Arthritis Res*, pp. 237-240). Note that the test for obviousness under 35 U.S.C. 103 requires a highly fact-dependent analysis involving taking the claimed subject matter as a whole and comparing it to the prior art. Like statins, side-chain oxysterols are HMG-CoA reductase inhibitors. Consequently, based on the teachings in the prior art as a whole, one would expect that like statins treatment enhances bone growth and differentiation of osteo-progenitor human cells, side-chain oxysterols would also be promoting bone differentiation.

Regarding 6) applicants' arguments are not persuasive as they rely on limitations, e.g., "Unlike these statins, oxysterols do not exert their osteogenic effect via the expression of BMP, but rather function via aspects of the hedgehog pathway, that are not present in the claims.

At pages12-13 of the remarks insofar as the disclosure of Parish and Wang, Applicants essentially argue that: 1) Parish does not mention osteoblastic differentiation, 2) Parish does not remedy the defect of Paralkar in that it fails to show that an oxysterol (or, for that matter, any particular inhibitor of HMG-CoA reductase) would be expected to induce osteoblastic differentiation, 3) Parish does not teach or suggest that an inhibitor of HMG-CoA reductase can inhibit adipocyte differentiation of mammalian mesenchymal stem cells (as is required by claim 1), 4) Wang is directed to the effects of a statin, and does not suggest or disclose that an oxysterol could substitute for the statin, e.g., induce osteoblastic differentiation, 5) Wang does not teach or suggest that an oxysterol could be substituted for the statin to induce osteoblastic differentiation, and 6) Wang does not directly test the ability of lovastatin to inhibit adipocyte differentiation

and to induce osteoblastic differentiation of MSCs but rather demonstrates that if steroids cause osteonecrosis in animals by inducing the death of osteoblasts, then statins could reverse this effect by inhibiting osteoblast death and not stimulating osteogenesis. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), 2), 3), 4) and 5), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). None of the references has to teach each and every claim limitation. If they did, this would have been anticipation and not an obviousness-type rejection.

Regarding 6), Wang clearly discloses what was well known in the art at the time the invention was made in relation to the lipid lowering agent, lovastatin. That is lovastatin is an inhibitor of hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase (p. 307, col. 2, paragraph 2). Suppressors of HMG-CoA) reductase markedly reduce sterol biosynthesis (Parish, 1995, p. 247, col. 2) including synthesis of cholesterol. Administration of a cholesterol agonist dexamethasone to MSCs reduces osteoblast differentiation (e.g., reduction of Type I collagen and osteocalcin mRNA) while promoting differentiation of MSCs into adipocytes (Wang, p. 295, col. 1 bridging to col. 2, first paragraph). Reduction of cholesterol synthesis by administration of lovastatin reverses the effect of dexamethasone on differentiation of precursor cells in bone marrow to adipocytes. Wang concludes, "Lovastatin also inhibits the expression of a fat specific gene [422(aP2)] by more marrow osteoprogenitor cells, while it maintains their

osteoblastic phenotype, indicating that lovastatin benefits the balance of the marrow microenvironment by keeping a proper ratio of marrowfat, hematopoietic tissues and bone" (Wang, p. 307, col. 2, last paragraph). Hence, the publication of Wang clearly discloses that by lowering sterol synthesis in MSCs-bone forming cells, the osteoblastic phenotype is maintained. The substitution of human MG-63 bone cells (i.e., osteo-progenitor human osteoblast) of Paralkar for mouse MSCs (e.g., pluripotent mesenchymal cells, D1) would have yielded the predictable results to one of ordinary skill in the art at the time of the invention of inducing the osteoblastic phenotype and inhibiting adipocyte differentiation by lowering sterol synthesis with HMG-CoA reductase inhibitors.

For the reasons set forth above, Applicant's arguments and the Parhami Declaration are not found persuasive. Based on the teachings in the prior art as a whole, one of skill in the art would have found the claimed invention *prima facie* obvious.

Provisional Rejection, Obviousness Type Double Patenting-

Claims 1-3, 6-8, 11-17, 19-21, 23-26 and 28 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-9, 11-15, 17-20, 22-25 and 27-30 of copending Application No. 10,569,994, in view of Paralkar et al., 20040176423 (Date of Publication September 9, 2004), for the reasons already of record as set forth in the office action of 06-11-2008.

Applicants have not properly address the specific grounds of rejection as discussed in the previous office action setting.

Claims 1-3, 6-8, 11-17, 19-21, 23-26 and 28 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over

claims 1-11 of copending Application No. 11/918,089 and over claims 1-9 and 15 of the copending Application No. 11/991,322, for the reasons already of record as set forth in the office action of 06-11-2008.

Applicants have not properly address the specific grounds of rejection as discussed in the previous office action setting.

New grounds of objection

Claim objection

Claims 2, 7, 16 and 25 objected to because of the following informalities: The word "pregnenolone" is misspelled. Appropriate correction is required.

Notice of Non-Compliant Amendment (37 CFR 1.121)

The amendment to the claims filed on 09-23-2009 does not comply with the requirements of 37 CFR 1.121(c) because the text of currently amended claim 22 filed on 09-23-2009 is not identified with the proper status in the claim listing as "currently amended withdrawn".

Of note, claim 22, which depends on claim 19, comprises administration to a patient of at least a secondary agent. Applicants' elected without traverse to prosecute the species bisphosphonates as the secondary agent reading on claims 23 and 28 (see page 2 of Applicants' response of 03-31-2008) in Applicants' response filed on 03-31-2008. Accordingly, claim 22 was withdrawn from further consideration by the Examiner pursuant to 37 CFR 1.142(b), as being drawn to nonelected species, as evidenced by the fact that claim 22 has not included in claims being examined for prosecution on the merits in the previous Office actions of 06-11-2008 and 03-23-2009. Upon the allowance

of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Amendments to the claims filed on or after 09-23-2009 must comply with 37 CFR 1.121(c) which states:

(c) *Claims*. Amendments to a claim must be made by rewriting the entire claim with all changes (*e.g.*, additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

(2) *When claim text with markings is required.* All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended," and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer

consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of "currently amended," or "withdrawn" if also being amended, shall include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn-currently amended."

Any further claim amendments must comply with 37 CFR 1.121(c) or they may not be entered.

Conclusion

Claims 1-3, 6-8, 11-17, 19-21, 23-26 and 28 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

Maria Leavitt
Primary Examiner, Art Unit 1633